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SECONDHAND SMOKE EXPOSURE IN ADULTHOOD AND RISK OF LUNG CANCER AMONG NEVER SMOKERS: A POOLED ANALYSIS OF TWO LARGE STUDIES

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The interpretation of the evidence linking exposure to secondhand smoke with lung cancer is constrained by the imprecision of risk estimates. The objective of the study was to obtain precise and valid estimates of the risk of lung cancer in never smokers following exposure to secondhand smoke, including adjustment for potential confounders and exposure misclassification. Pooled analysis of data from 2 previously reported large case-control studies was used. Subjects included 1,263 never smoking lung cancer patients and 2,740 population and hospital controls recruited during 1985–1994 from 5 metropolitan areas in the United States, 11 areas in Germany, Italy, Sweden, United Kingdom, France, Spain and Portugal. Odds ratios (ORs) of lung cancer were calculated for ever exposure and duration of exposure to secondhand smoke from spouse, workplace and social sources. The OR for ever exposure to spousal smoking was 1.18 (95% CI = 1.01–1.37) and for long-term exposure was 1.23 (95% CI = 1.01–1.51). After exclusion of proxy interviews, the OR for ever exposure from the workplace was 1.16 (95% CI = 0.99–1.36) and for long-term exposure was 1.27 (95% CI = 1.03–1.57). Similar results were obtained for exposure from social settings and for exposure from combined sources. A dose-response relationship was present with increasing duration of exposure to secondhand smoke for all 3 sources, with an OR of 1.32 (95% CI = 1.10–1.79) for the long-term exposure from all sources. There was no evidence of confounding by employment in high-risk occupations, education or low vegetable intake. Sensitivity analysis for the effects of misclassification (both positive and negative) indicated that the observed risks are likely to underestimate the true risk. Clear dose-response relationships consistent with a causal association were observed between exposure to secondhand smoke from spousal, workplace and social sources and the development of lung cancer among never smokers.

Key words: *lung cancer; secondhand smoke*

More than 50 studies based on over 7,300 nonsmoking lung cancer cases have examined the association between exposure to secondhand smoke and the risk of lung cancer in lifelong nonsmokers.[1] Recent systematic reviews identified an excess risk of lung cancer of the order of 24% in nonsmokers who lived with a smoker, which could not be explained by chance, potential biases or confounding.[1,2] Although heterogeneity exists in the study-

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specific results, there is a marked consistency in the risk estimates for men and women and by study design, with both cohort and case-control studies yielding similar summary risk estimates. Moreover, a recent international working group of 29 experts convened by the IARC Monographs Program concluded that secondhand smoke is carcinogenic to humans.[3]

Despite the amount of evidence available, there is uncertainty regarding the actual level of the increased risk with increasing dose, as well as the level of the increased risk from other sources, including social and workplace settings. We have therefore undertaken a pooled analysis of the data from the 2 largest studies to measure the relationship between secondhand smoke and lung cancer. The aims of this combined analysis were to obtain a more precise estimate of the role of secondhand smoke from spousal, workplace and social sources from individual level data, to estimate the effect of potential confounders including dietary effects and workplace exposure to other lung carcinogens and to conduct a sensitivity analysis concerning the potential effect of exposure misclassification.

MATERIAL AND METHODS

The analysis included cases of lung cancer and controls enrolled in 2 case-control studies conducted in the United States and in Europe. The methods used in both studies have been previously described in detail[4,5] and are briefly summarized here.

U.S. study

The U.S. study was a population-based case-control study carried out in 5 metropolitan areas: Atlanta, Georgia (4 counties); New Orleans, Louisiana (3 parishes); Houston, Texas (2 counties); Los Angeles, California (1 county); and San Francisco Bay Area, California (6 counties). Cases were women resident of the study areas diagnosed with a microscopically confirmed primary lung cancer during 1985–1990 (1985–1988 in Atlanta and Houston), aged 20–79 at diagnosis, able to speak English, Spanish or Chinese, with no history of previous cancer, who smoked less than 100 cigarettes in their lifetime. Controls were selected via random digit dialing, supplemented, for women aged 65–79, by random sampling from files of the Health Care Financing Administration. Two controls were frequency matched to each case on age group, ethnicity and study area. The selection criteria described above for cases were also applied to controls. The project was approved by an institutional review board within each center.

Interviews were conducted with 665 out of 800 potential cases (including 241 interviews with next of kin; response rate, 83%) and 1,278 out of 1,826 potential controls (no interviews with next of kin; response rate, 70%). The questionnaire was primarily aimed at assessing exposure to secondhand smoke during childhood (up to age 18) and in adult life from spouses, other household members and occupational and social sources. For household members, information was sought on duration of exposure and the type of tobacco product. The daily amounts smoked by household members including spouses were also elicited. Only duration of exposure was elicited for occupational and social sources of exposure. Information was also obtained on other potential causes of lung cancer, including dietary factors, family history of cancer and workplace exposure to occupational carcinogens.

Urine samples were obtained from 53% of cases and 83% of controls and were analyzed for cotinine level. Two cases and 25 controls had a urinary cotinine/creatinine ratio above 99 ng/mg and were excluded. An additional 9 cases and 25 controls had levels in the 55–99 ng/mg range, compatible with high exposure to secondhand smoke. A central pathology review was conducted on samples from 85% of cases: the diagnosis was confirmed for 98% of them, and the 10 cases with unconfirmed diagnosis were excluded. Previous results have been based on the analysis of data from 653 cases and 1,253 controls.

European study

The European study was conducted as a population-based case-control study in Germany (3 areas: Bremen and Frankfurt; Thuringia and Saxony; parts of North Rhine-Westphalia, Eifel and Saarland), Italy (2 areas: Turin; parts of Veneto) and Sweden (Stockholm) and as a hospital-based case-control study in Italy (1 hospital in Rome), Spain (10 hospitals in Barcelona), France (12 hospitals, mainly in Paris) and Portugal (2 areas: 3 hospitals in Lisbon; 1 hospital in Porto). The center in the United Kingdom (Devon and Cornwall) included both hospital and population controls. Cases were men and women either resident of the study areas or referred to the participating hospitals who were diagnosed with a primary lung cancer during 1988–1994, aged up to 75, and who smoked less than 400 cigarettes in their lifetime. Population-based controls were selected via random sampling from population registries and hospital-based controls were selected among patients admitted to the same hospitals as the cases, excluding those with tobacco-related diseases. Controls were frequency matched to cases for age, sex and region of residence. There were differences among centers regarding restriction to microscopically confirmed cases, list of eligible diseases of hospital controls and inclusion of subjects above age 75. The project was approved by an institutional review board within each center.

No interviews were conducted with next of kin. The questionnaire on secondhand smoke was very similar to the one used in the American study. Information comparable to that of the American study was also collected on occupational exposures and diet (the latter in 8 centers). No validation of nonsmoking status was conducted via urinary cotinine measurement. In 3 centers, cross-interviews were conducted with next of kin for a subset of cases and controls in order to validate both the nonsmoking status of the index subjects and their exposure to secondhand smoke from the spouse. Nonsmoking status was not confirmed for 1/175 cases and 4/233 controls. No central pathology review was conducted. Previous results have been based on the analysis of data from 650 cases and 1,542 controls.

Pooled analysis

The data included in this pooled analysis differ slightly from those that previous published results were based on. First, the data from the area in Lisbon were excluded (54 cases and 47 controls) because the local investigator was unable to participate in this analysis. Second, a common cut-point for the definition of never smokers in the 2 studies was adopted, of 100 cigarettes or equivalent amount from other tobacco products, resulting in the exclusion of 27 cases and 90 controls from the European study who had reported smoking between 101 and 400 cigarettes. Third, a common upper age limit of 79 was adopted, resulting in the inclusion of 34 cases and 69 controls from the European study aged 76–79. The final data set included 1,263 cases (653 from the American study, 610 from the European study) and 2,740 controls (1,253 and 1,487, respectively).

Further differences between the studies were evaluated by conducting sensitivity analyses after excluding 241 cases from the American study with next-of-kin interview; excluding 229 cases and 564 controls from European centers with hospital-based recruitment; and restricting analysis to women by excluding 121 male cases and 498 male controls from the European study.

The following variables were obtained from the original studies: age at diagnosis for cases or interview for controls (classified in 10-year groups), study center, sex, ever employment in high-risk occupations, education level (low, intermediate, high and unknown, based on country-specific classifications), vegetable intake, type of respondent (study subject and next of kin), type of subject recruitment (population- and hospital-based) and histologic type of lung cancer (adenocarcinoma, small and squamous cell carcinoma, other types). Tertiles of vegetable intake included a predefined list of common vegetables, fruits and vitamin supple-

ments in the American study, and a predefined list of common vegetables in the European study. High-risk occupations in the European study included a predefined list of occupations known to be associated with lung cancer.[6] The U.S. list involved those working for 5 years or more in 12 industries likely to involve exposure to lung carcinogens.

Spousal exposure to secondhand smoke was defined as ever having a spouse who smoked any tobacco product while they lived together, while smoke-years of exposure was defined as the number of years that the subject's spouse smoked while they were living together. Similarly, years of workplace exposure was defined as the total number of years in which the subject reported working in an environment where others were smoking, and smoke-years of social exposure was defined as the total number of years of exposure to tobacco smoke in places other than the home and the workplace (at least 2 hr per week in the U.S. study). Finally, in order to obtain a cumulative estimate of exposure to secondhand smoke, the sum of smoke-years from the 3 sources was calculated.

The statistical analysis was based on unconditional logistic regression modeling, resulting in the estimate of odds ratios (ORs) and 95% confidence intervals (CIs). For each source of secondhand smoke, individuals unexposed from that source formed the reference group. Tertiles for secondhand smoke exposure were calculated according to the distribution of the exposed control group for each exposure source separately (although this resulted in tertiles of exposure that are different for the 3 exposure sources). Information from each form of exposure was incomplete for a small number of subjects, although this was not imputed. Regression models included center, age and gender. In addition, models including also education level, exposure to occupational carcinogens and vegetable intake were fitted to test for their potential confounding effect. Linear trends were tested by fitting regression models with an ordinal exposure variable. Selected analyses were repeated after stratification for histologic type.

RESULTS

The distribution of the cases and controls by study center, age, sex and other demographic and study design variables is shown in Table I. The number of subjects included from the U.S. study is identical to the previous published analysis, whereas the number of subjects from the European study differs slightly due to the exclusion of one center and the more stringent criteria of a never smoker, and also by including cases and controls only up to 79 years of age. The U.S. subjects were generally older than the

TABLE I – SELECTED CHARACTERISTICS OF CASE AND CONTROL SUBJECTS

	European study				American study				Combined study			
	Controls (n = 1487)		Cases (n = 610)		Controls (n = 1253)		Cases (n = 653)		Controls (n = 2,740)		Cases (n = 1,263)	
	n	%	n	%	n	%	n	%	n	%	n	%
Study center												
Sweden	116	7.8%	77	12.6%					116	4.2%	77	6.1%
Germany 1	228	15.3%	76	12.5%					228	8.3%	76	6.0%
Germany 2	159	10.7%	141	23.1%					159	5.8%	141	11.2%
Germany 3	52	3.5%	30	4.9%					52	1.9%	30	2.4%
United Kingdom	140	9.4%	26	4.3%					140	5.1%	26	2.1%
France	139	9.3%	69	11.3%					139	5.1%	69	5.5%
Portugal 2	55	3.7%	35	5.7%					55	2.0%	35	2.8%
Spain	182	12.2%	81	13.3%					182	6.6%	81	6.4%
Italy 1	202	13.6%	40	6.6%					202	7.4%	40	3.2%
Italy 2	166	11.2%	17	2.8%					166	6.1%	17	1.3%
Italy 3	48	3.2%	18	3.0%					48	1.8%	18	1.4%
Atlanta					76	6.1%	46	7.0%	76	2.8%	46	3.6%
Houston					42	3.4%	41	6.3%	42	1.5%	41	3.2%
Los Angeles					512	40.9%	264	40.4%	512	18.7%	264	20.9%
Louisiana					57	4.5%	34	5.2%	57	2.1%	34	2.7%
San Francisco Bay Area					566	45.2%	268	41.0%	566	20.7%	268	21.2%
Age, years												
< 50	162	10.9%	70	11.5%	165	13.2%	70	10.7%	327	11.9%	140	11.1%
50–59	396	26.6%	158	25.9%	154	12.3%	110	16.8%	550	20.1%	268	21.2%
60–69	558	37.5%	218	35.7%	398	31.8%	213	32.6%	956	34.9%	431	34.1%
70–79	371	24.9%	164	26.9%	536	42.8%	260	39.8%	907	33.1%	424	33.6%
Gender												
Male	498	33.5%	121	19.8%					498	18.2%	121	9.6%
Female	989	66.5%	489	80.2%	1,253	100.0%	653	100.0%	2,242	81.8%	1,142	90.4%
High-risk occupations												
Nonexposed	1,419	95.4%	588	96.4%	1,216	97.0%	629	96.3%	2,635	96.2%	1,217	96.4%
Ever exposed	68	4.6%	22	3.6%	37	3.0%	24	3.7%	105	3.8%	46	3.6%
Education level												
Low	252	16.9%	55	9.0%	270	21.5%	108	16.5%	522	19.1%	163	12.9%
Intermediate	299	20.1%	96	15.7%	315	25.1%	99	15.2%	614	22.4%	195	15.4%
High	648	43.6%	309	50.7%	659	52.6%	433	66.3%	1,307	47.7%	742	58.7%
Unknown	288	19.4%	150	24.6%	9	0.7%	13	2.0%	297	10.8%	163	12.9%
Respondent												
Study subject	1,487	100.0%	610	100.0%	1,253	100.0%	412	63.1%	2,740	100.0%	1,022	80.9%
Next of kin							241	36.9%			241	19.1%
Type of recruitment												
Population-based	923	62.1%	381	62.5%	1,253	100.0%	653	100.0%	2,176	79.4%	1,034	81.9%
Hospital-based	564	37.9%	229	37.5%					564	20.6%	229	18.1%
Histological type												
Adenocarcinoma			311	51.0%			497	76.1%			808	64.0%
Small and squamous cell			162	26.6%			64	9.8%			226	17.9%
Other types			137	22.5%			92	14.1%			229	18.1%

European subjects: the proportion of subjects who reported working in high-risk occupations was less than 5% in both studies. Histologic type also differed between the 2 regions with a higher proportion of adenocarcinomas in the United States.

The OR of lung cancer associated with ever exposure to spousal tobacco smoke was 1.18 (95% CI = 1.01–1.37) (Table II). There was some evidence of a dose-response relationship with duration of exposure ($p = 0.07$), with highest risk being observed in the upper tertile of exposure, corresponding to more than 30.9 years (OR = 1.23; 95% CI = 1.01–1.51). The risk in the high-exposure group was similar for adenocarcinoma (OR = 1.24; 95% CI = 0.98–1.57) and small and squamous cell carcinoma (OR = 1.26; 95% CI = 0.84–1.90). Results were similar when proxy interviews were excluded from the analysis, although the exclusion of data from hospital-based centers resulted in a more statistically significant dose-response relationship ($p = 0.04$) and increased risk in the upper tertile of exposure (OR = 1.30; 95% CI = 1.04–1.63).

An excess risk was observed for ever exposure to secondhand smoke in the workplace (OR = 1.13; 95% CI = 0.97–1.31) and, when analyzed by duration of exposure, a dose-response effect was observed ($p = 0.01$) with a significant increased risk in the upper tertile, corresponding to more than 21 years of exposure (OR = 1.25; 95% CI = 1.03–1.51; Table III). When proxy cases were excluded from the analysis, the overall increased risk was 1.16 (95% CI = 0.99–1.36), and in the upper tertile it was 1.27 (95% CI = 1.03–1.57).

An increase in risk was observed for those who reported ever exposure to secondhand smoke in social settings (OR = 1.17; 95% CI = 1.00–1.36), and a dose-response effect was detected with duration of exposure ($p = 0.02$), with the largest increase in risk in the highest exposed group corresponding to more than 20 years of exposure (OR = 1.26; 95% CI = 1.01–1.58; Table IV). When stratified by histologic type, the increased risk in the highest exposed group was more apparent for small and squamous cell carcinoma (OR = 1.54; 95% CI = 1.01–2.34) than for adenocarcinoma (OR = 1.26; 95% CI = 0.97–1.64).

A similar pattern was observed for an analysis of any exposure to secondhand smoke from spousal, workplace or social sources combined (OR = 1.22; 95% CI = 0.99–1.51), along with a dose-response effect ($p = 0.01$) with the greatest risk in the highest exposure category (OR = 1.32; 95% CI = 1.04–1.66; Table V). Restricting the analysis to study subject interviews made little difference, although a more marked overall effect was observed when hospital controls were excluded (OR = 1.31; 95% CI = 1.03–1.67).

Results of the analysis restricted to women are practically identical to those reported in Tables II to V and are not presented in detail. The results reported in Tables II to V were subsequently controlled for employment in high-risk occupations in addition to education level and vegetable consumption. However, results were similar when the potential confounders were either included or excluded from the regression models. For example, the OR for ever exposure from any of the 3 sources combined was exactly the same at 1.22 (95% CI = 0.99–1.51) when potential confounders were included or excluded, confirming the lack of any apparent confounding.

DISCUSSION

This pooled analysis of 2 large studies of secondhand smoke and lung cancer provides firm evidence for a dose-response relationship between lung cancer risk and duration of exposure to secondhand smoke for the 3 main sources of exposure: spousal, workplace and social. The estimate of the increased risk is 18% (95% CI = 1–37) in those ever exposed to spousal secondhand smoke and is 23% (95% CI = 1–51) in the long-term exposed. Increased risks for long-term exposure to secondhand smoke were also observed for workplace exposure (OR = 1.25; 95% CI = 1.03–1.51) and social exposure (OR = 1.26; 95% CI = 1.01–1.58).

Metaanalyses of lung cancer and secondhand smoke have been criticized for the potential lack of standardization in defining exposure and the potential for publication bias.[7] Our pooled analysis also offers several advantages over previous metaanalyses, and in particular we have been able to ensure a similar definition of nonsmoker for all subjects. We have also been able to conduct an analysis with identical exposure categories for each of the exposure sources, and we have been able to adjust for similar potential confounding variables, including diet, occupation and educational level. The inclusion or exclusion of these potential confounding variables did not influence the results, indicating no confounding effect in any direction from these sources. Our results provide more conservative estimates of the increased risk of exposure to secondhand smoke than a previous metaanalysis, which

TABLE II – ODDS RATIOS OF LUNG CANCER FROM EXPOSURE TO SECONDHAND SMOKE FROM THE SPOUSE, ANY TYPE OF TOBACCO

Cases	All subjects				Study subjects interviews only				Population controls only			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Ever exposed												
No	496	1,277	1.00		421	1,277	1.00		404	1,043	1.00	
Yes	764	1,458	1.18	1.01–1.37	600	1,458	1.16	0.99–1.36	627	1,133	1.19	1.01–1.40
Duration of exposure (years)												
Nonexposed	496	1,277	1.00		421	1,277	1.00		404	1,043	1.00	
< 16	246	457	1.18	0.97–1.44	194	457	1.19	0.96–1.47	212	387	1.17	0.95–1.45
16–30.9	224	480	1.05	0.86–1.29	173	480	1.01	0.81–1.26	190	385	1.06	0.85–1.32
≥ 31.0	264	491	1.23	1.01–1.51	211	491	1.24	1.00–1.54	211	348	1.30	1.04–1.63
Trend[a]			0.07				0.11				0.04	
Adenocarcinoma												
Nonexposed	306	1,277	1.00		259	1,277	1.00		260	1,043	1.00	
< 16	163	457	1.14	0.90–1.43	129	457	1.14	0.89–1.46	144	387	1.13	0.88–1.45
16–30.9	149	480	1.08	0.85–1.37	109	480	0.98	0.76–1.28	136	385	1.12	0.87–1.45
≥ 31.0	170	491	1.24	0.98–1.57	134	491	1.24	0.96–1.60	144	348	1.30	1.01–1.69
Trend			0.10				0.20				0.05	
Small and squamous cell												
Nonexposed	96	1,277	1.00		84	1,277	1.00		80	1,043	1.00	
< 16	38	457	1.22	0.80–1.85	32	457	1.32	0.83–2.08	32	387	1.20	0.76–1.89
16–30.9	42	480	1.11	0.74–1.67	37	480	1.17	0.75–1.82	31	385	0.96	0.60–1.53
≥ 31.0	45	491	1.26	0.84–1.90	39	491	1.33	0.85–2.07	32	348	1.26	0.78–2.02
Trend			0.30				0.23				0.52	

All ORs adjusted by age, center, gender.–[a]p-value for linear trend.

TABLE III – ODDS RATIOS OF LUNG CANCER FROM EXPOSURE TO SECONDHAND SMOKE FROM WORKPLACE

	All subjects				Study subjects interviews only				Population controls only			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Ever exposed												
No	490	1174	1.00		410	1,174	1.00		363	857	1.00	
Yes	729	1560	1.13	0.97–1.31	610	1,560	1.16	0.99–1.36	627	1,313	1.11	0.94–1.31
Duration of exposure (years)												
Nonexposed	490	1174	1.00		410	1,174	1.00		363	857	1.00	
< 8.0	198	472	0.94	0.76–1.15	169	472	1.00	0.80–1.26	179	406	0.95	0.75–1.18
8.0–20.9	267	544	1.17	0.97–1.42	220	544	1.19	0.97–1.46	220	454	1.11	0.89–1.37
≥ 21.0	262	543	1.25	1.03–1.51	219	543	1.27	1.03–1.57	228	453	1.29	1.04–1.59
Trend[a]			0.01				0.01				0.02	
Adenocarcinoma												
Nonexposed	300	1174	1.00		246	1,174	1.00		236	857	1.00	
< 8.0	133	472	0.95	0.74–1.21	110	472	0.99	0.76–1.29	126	406	0.99	0.77–1.29
8.0–20.9	178	544	1.20	0.96–1.50	147	544	1.24	0.97–1.58	150	454	1.13	0.88–1.45
≥ 21.0	164	543	1.20	0.95–1.51	139	543	1.27	0.99–1.62	150	453	1.27	0.99–1.63
Trend			0.05				0.05				0.05	
Small and squamous cell												
Nonexposed	92	1174	1.00		82	1,174	1.00		64	857	1.00	
< 8.0	36	472	0.96	0.62–1.47	33	472	1.04	0.66–1.63	31	406	0.95	0.59–1.53
8.0–20.9	40	544	0.98	0.65–1.48	35	544	1.02	0.66–1.58	35	454	1.03	0.65–1.63
≥ 21.0	51	543	1.36	0.92–2.00	46	543	1.41	0.93–2.13	40	453	1.31	0.84–2.05
Trend			0.19				0.16				0.28	

All ORs adjusted by age, center, gender.–[a]*p*-value for linear trend.

TABLE IV – ODDS RATIOS OF LUNG CANCER FROM EXPOSURE TO SECONDHAND SMOKE FROM SOCIAL EXPOSURE

	All subjects				Study subjects interviews only				Population controls only			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Ever exposed												
No	818	1,827	1.00		666	1,827	1.00		669	1,476	1.00	
Yes	407	904	1.17	1.00–1.36	349	904	1.17	0.99–1.37	327	691	1.22	1.03–1.45
Duration of exposure (years)												
Nonexposed	818	1,827	1.00		666	1,827	1.00		669	1,476	1.00	
< 8.0	123	287	1.04	0.84–1.32	105	287	1.05	0.82–1.35	101	221	1.08	0.83–1.41
8.0–19.9	128	290	1.20	0.95–1.52	114	290	1.21	0.95–1.56	104	217	1.30	0.99–1.70
≥ 20.0	154	320	1.26	1.01–1.58	128	320	1.24	0.98–1.58	121	248	1.30	1.01–1.67
Trend[a]			0.02				0.03				0.01	
Adenocarcinoma												
Nonexposed	530	1,827	1.00		427	1,827	1.00		454	1,476	1.00	
< 8.0	70	287	0.92	0.69–1.24	60	287	0.94	0.69–1.29	59	221	0.93	0.67–1.28
8.0–19.9	85	290	1.30	0.99–1.72	74	290	1.31	0.98–1.76	72	217	1.38	1.02–1.88
≥ 20.0	95	320	1.26	0.97–1.64	79	320	1.28	0.96–1.69	81	248	1.30	0.97–1.73
Trend			0.03				0.04				0.03	
Small and squamous cell												
Nonexposed	139	1,827	1.00		120	1,827	1.00		110	1,476	1.00	
< 8.0	28	287	1.33	0.85–2.08	25	287	1.38	0.86–2.22	24	221	1.50	0.92–2.47
8.0–19.9	23	290	1.04	0.64–1.70	22	290	1.09	0.66–1.80	17	217	1.02	0.58–1.80
≥ 20.0	33	320	1.54	1.01–2.34	29	320	1.52	0.97–2.38	22	248	1.39	0.83–2.30
Trend			0.07				0.08				0.23	

All ORs adjusted by age, center, gender.–[a]*p*-value for linear trend.

reported an overall increase of 24% (95% CI = 13–36) for spousal exposure and 39% (95% CI = 15–68) for occupational exposure.[2,8] The confidence intervals from the pooled analysis do, however, include the higher odds ratios obtained from previous metaanalyses, indicating that the results are broadly consistent with each other.

Misclassification of exposure to secondhand smoke is inevitable and, assuming that it is nondifferential with respect to case/control status, will dilute the estimate of the effect. The substantial proportion of U.S. cases for whom information was obtained from their next of kin is a potential source of differential misclassification. When these cases are removed from the analysis, it is of interest that the odds ratio for ever exposure does not change substantially for any of the sources of exposure.

Concerning historical exposure to secondhand smoke, some exposure is likely to be inevitable, resulting in an unexposed group who will have been exposed to some extent. A previous validity study found that over 60% of nonsmokers who reported no exposure to secondhand smoke from spousal or workplace sources had detectable levels of urinary cotinine.[9] One approach to estimating the risk of exposure to secondhand smoke when compared to a true never-exposed group, which was adopted in a recent metaanalysis,[2] was based on the observation of 3 times higher cotinine levels in nonsmokers living with a smoker as opposed to nonsmokers living with a nonsmoker. Assuming that the observed relative risk is equal to $(1 + 3x)/(1 + x)$, where x is the background exposure level of secondhand smoke for nonexposed subjects, and adopting test-based confidence intervals, this results in an estimate of adjusted true OR of 1.30 (95% CI = 1.11–1.51) for ever exposure to spousal smoking.

The other form of misclassification, that of previous smokers classifying themselves as nonsmokers, may work in the opposite fashion to increase the risk estimate artificially. The proportion of reported never smokers with cotinine levels consistent with current

TABLE V - ODDS RATIOS OF LUNG CANCER FROM EXPOSURE TO SECONDHAND SMOKE FROM SPOUSE, WORKPLACE AND SOCIAL EXPOSURE

	All subjects				Study subjects interviews only				Population controls only			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Ever exposed												
No	146	383	1.00		125	383	1.00		108	298	1.00	
Yes	1,102	2,351	1.22	0.99–1.51	896	2,351	1.18	0.94–1.48	911	1,874	1.31	1.03–1.67
Duration of exposure (in years)												
Nonexposed	146	383	1.00		125	383	1.00		108	298	1.00	
< 20.0	329	752	1.09	0.86–1.39	262	752	1.03	0.80–1.33	281	629	1.16	0.88–1.52
20.0–38.9	348	768	1.21	0.96–1.54	299	768	1.24	0.96–1.59	275	612	1.25	0.95–1.64
≥ 39.0	413	817	1.32	1.04–1.66	327	817	1.25	0.97–1.60	349	623	1.50	1.15–1.96
Trend[a]			0.01				0.02				0.00	
Adenocarcinoma												
Nonexposed	91	383	1.00		77	383	1.00		71	298	1.00	
< 20.0	210	752	1.03	0.77–1.37	164	752	0.96	0.70–1.31	183	629	1.09	0.79–1.50
20.0–38.9	222	768	1.18	0.89–1.57	192	768	1.22	0.90–1.65	186	612	1.25	0.91–1.71
≥ 39.0	269	817	1.30	0.98–1.71	208	817	1.22	0.90–1.65	241	623	1.50	1.10–2.05
Trend			0.02				0.05				0.00	
Small and squamous cell												
Nonexposed	26	383	1.00		22	383	1.00		21	298	1.00	
< 20.0	57	752	1.26	0.76–2.08	50	752	1.38	0.80–2.38	48	629	1.20	0.68–2.11
20.0–38.9	65	768	1.48	0.90–2.42	57	768	1.60	0.94–2.74	52	612	1.41	0.81–2.47
≥ 39.0	75	817	1.52	0.93–2.47	66	817	1.63	0.96–2.77	54	623	1.38	0.79–2.40
Trend			0.08				0.07				0.23	

All ORs adjusted by age, center, gender.—[a]*p*-value for linear trend.

smoking has consistently been found to be approximately 2%.[9–15] although this figure is likely to be lower in the current study given the cotinine analysis conducted on the majority of cases and controls in the American study and the next-of-kin verification conducted on a sample of subjects in the European study. The proportion of former smokers classifying themselves as never smokers is harder to estimate. Overall, such misclassified cases are likely to consist of light smokers and long-term quitters and have a correspondingly low relative risk of lung cancer when compared to current smokers. The likely relative risk for misclassified never smokers has been estimated to be approximately 3-fold when compared to true never smokers.[2] Even if we assume that in the current study, in addition to 2% of the subjects being true current smokers, there are an extra 5% being true ex-smokers, and that smokers are 3 times more likely to marry other smokers, the effect on the reported odds ratio for ever exposure to spousal secondhand smoke will not be large. Adopting the method by Hackshaw *et al.*,[2] the effect will be to reduce our adjusted OR from 1.30 (95% CI = 1.11–1.51) to 1.24 (95% CI = 1.06–1.44), still above the observed OR for ever spousal exposure of 1.18 (95% CI = 1.01–1.37). Therefore, the increase in the odds ratio potentially caused by this type of misclassification is likely to be outweighed by the attenuation caused by exposure to secondhand smoke from subjects classified as nonexposed.

Other forms of bias that may influence the results of our pooled analysis are the inclusion of hospital-based controls and the collection of exposure information from next-of-kin interviews. However, we have conducted subgroup analyses to address these potential sources of bias. Results were generally higher when proxy interviews were excluded, especially for workplace exposure, and also for social exposure when analysis was restricted to population controls. It is therefore likely that there is some attenuation in the risk estimates for the main analysis, which incorporates cases with proxy interviews and data from hospital-based centers.

Our results according to histologic type of lung cancer suggest an increased risk of both adenocarcinoma and squamous/small cell carcinomas from all 3 sources of exposure. For example, when all 3 sources are combined, a consistent dose response with duration of exposure is seen for both histologic types with a higher risk for squamous and small cell carcinomas apparent for each tertile. Although these results should be interpreted with caution, given the lack of a central pathologic review in the European study and the inconsistency of this finding when just restricted to centers that recruited population controls, they are broadly compatible with the stronger association between active smoking and small and squamous cell carcinomas as opposed to adenocarcinoma.[16]

In conclusion, our pooled analysis provides more precise estimates of the effect of secondhand smoke on lung cancer risk in nonsmokers from all sources than those previously obtained in individual studies and emphasizes the importance of protecting nonsmokers from secondhand smoke. The implications of reducing exposure to secondhand smoke, however, go beyond the prevention of lung cancer in nonsmokers, since such measures to reduce exposure to secondhand smoke also result in a decreased opportunity for smoking among active smokers and a subsequent reduction in active smoking levels.[17]

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